Troponin T levels in patients with acute heart failure: clinical and prognostic significance of their detection and release during hospitalisation

Marco Metra, Luca Bettari, Franca Pagani, Valentina Lazzarini, Carlo Lombardi, Valentina Carubelli, Graziella Bonetti, Silvia Bugatti, et al.

Clinical Research in Cardiology

ISSN 1861-0684

Clin Res Cardiol
DOI 10.1007/s00392-012-0441-5

Springer

Clin Res Cardiol
DOI 10.1007/s00392-012-0441-5

ORIGINAL PAPER

Troponin T levels in patients with acute heart failure: clinical and prognostic significance of their detection and release during hospitalisation

Marco Metra · Luca Bettari · Franca Pagani · Valentina Lazzarini · Carlo Lombardi · Valentina Carubelli · Graziella Bonetti · Silvia Bugatti · Giovanni Parrinello · Luigi Caimi · G. Michael Felker · Livio Dei Cas

Received: 13 May 2011 / Accepted: 1 March 2012

Abstract
Aims Myocardial injury during an episode of acute heart failure (AHF) may be important for patents' outcome. We hypothesised that an increase of cardiac troponin levels (cTnT) during hospitalisation, in patients with undetectable levels on admission (cTnT release), may be a more specific marker of myocardial damage. With this aim, we assessed the clinical and prognostic significance of high serum cTnT levels at the time of admission and that of cTnT release in 198 consecutive patients admitted for AHF and with no signs of acute coronary syndrome.
Methods and results cTnT levels were serially measured at the time of admission, and after 6 and 12 h, in 198 consecutive patients admitted for AHF and with no signs of acute coronary syndrome. cTnT was detectable (>0.01 ng/mL) in 102 patients (52 %) and positive for myocardial necrosis (>0.03 ng/mL) in 78 patients (39 %). Negative cTnT at the time of admission became positive at 6 and/or 12 h in 36 (18 %) patients. Patients with increased cTnT levels were more likely to have coronary artery disease, hypertension, diabetes, and renal dysfunction. During a median follow-up duration of 247 days (IQR 96–480 days), the detection of increased cTnT levels was associated with a higher rate of all-cause deaths and, for cTnT release, all-cause death and cardiovascular rehospitalisation rate. CTnT release was an independent predictor of all-cause death and cardiovascular rehospitalisation, along with glomerular filtration rate, and the administration of inotropic agents during the initial hospitalisation.
Conclusions Increased cTnT levels are a frequent finding in patients with AHF. They are more likely to occur in patients with comorbidities and are associated with poorer outcomes. cTnT release is an independent predictor of poorer outcomes.

Keywords Acute heart failure · Troponin · Prognosis

M. Metra (✉) · L. Bettari · V. Lazzarini · C. Lombardi · V. Carubelli · S. Bugatti · L. Dei Cas
Cardiology, Department of Experimental and Applied Medicine, University and Civil Hospital of Brescia, c/o Spedali Civili, Piazza Spedali Civili 1, 25123 Brescia, Italy
e-mail: metramarco@libero.it

F. Pagani · G. Bonetti · L. Caimi
Laboratory of Biotechnology, Department of Biomedical Science and Diagnostics, University and Civil Hospital of Brescia, Brescia, Italy

G. Parrinello
Section of Medical Statistics and Biometry, Department of Biotechnologies and Biomedical Sciences, University of Brescia, Brescia, Italy

G. M. Felker
Duke Clinical Research Institute, Duke University Medical Center, Durham, NC, USA

Introduction

Acute heart failure (AHF) is the most frequent cause of hospitalisation in patients over 65 years of age [1, 2]. It is associated with severe symptoms and a poor prognosis, with an in-hospital mortality ranging from 3 to 7 %, and mortality rates of 5–15 %, and rehospitalisation rates of 30 % in the 3-6 months after discharge [1–3].

The mechanisms leading to the high event rate in patients with AHF are still incompletely understood. Acute myocardial damage is one of the most likely mechanisms [2–5]. Increased left ventricular filling pressure and myocardial stress, hypotension, tachycardia, endothelial dysfunction, platelet aggregation, activation of neurohormonal and

Published online: 10 March 2012

inflammatory mechanisms, oxidative stress, and altered calcium handling may all favour myocytes injury, necrosis or apoptosis, and/or troponin release even in patients with angiographically normal coronary arteries [3, 6].

The clinical relevance of these mechanisms is suggested by studies based on plasma troponins measurements. An increase of plasma troponin levels has been reported in 30–70 % of patients admitted for AHF, when traditional methods are used [7–16], and up to 90-100 % of the patients when high sensitivity assays are used [16, 17]. Such an increase in troponin levels is associated with a poor prognosis with a dose response relationship between the magnitude of the increase in circulating troponins and prognosis [11, 13, 16]. However, these studies are heterogeneous with respect of the patients studied, the criteria for the diagnosis of AHF and the cut-off levels for the definition of a significant increase in troponin levels.

In addition, previous studies, with only a few exceptions [10, 12, 16, 17], were based on only a single measurement taken at the time of admission to the hospital. However, the myocardial damage detected by an increase in serum troponin levels at the time of admission may be either pre-existent, and possibly contributing to the episode of acute decompensation, or secondary to the AHF itself. [6, 17–19] This condition may be different from that of an increase in serum troponin levels occurring during the hospitalisation in patients with undetectable levels at the time of admission (troponin release). This second event should be more specific for an acute myocardial damage secondary to the episode of acute decompensation. It is, therefore, important to detect an acute myocardial damage related to the AHF episode and, with this aim, measurement of serum troponin concentrations in serially drawn blood samples has been recently recommended [20].

The aim of this study was to assess the clinical and prognostic significance of the detection of high serum cardiac troponin T (cTnT) levels at the time of admission and that of their increase during hospitalisation, when undetectable on admission (cTnT release) in consecutive patients hospitalised for AHF and with no signs of acute coronary syndrome (ACS). We hypothesised that cTnT release might have been a more specific marker of myocardial damage related to, if not caused by, the AHF episode showing a greater prognostic power compared with increased cTnT at the time of admission.

Methods

Patients

This was a prospective, observational study in patients admitted with a diagnosis of AHF at the Institute of Cardiology of the University of Brescia. AHF was diagnosed on the basis of the criteria of the European Society of Cardiology as a rapid onset or change in the signs and symptoms of HF, resulting in the need for urgent therapy [1]. Treatment with ≥40 mg of furosemide administered intravenously was required as an inclusion criterion. Patients with ACS, myocarditis, cardiac tamponade, aortic dissection or evidence of non-cardiovascular factors as the main cause of symptoms were excluded. According to the universal definition of acute myocardial infarction, the diagnosis of ACS was made on the basis of concomitant typical symptoms and ECG changes indicative of myocardial ischaemia (new ST-T changes or new LBBB) and/or development of pathological Q-waves and/or imaging evidence of a new regional wall motion abnormality [21]. These patients were excluded from our study.

All patients underwent complete clinical examination at the time of hospital admission, and, on at least a daily basis, thereafter, until the time of hospital discharge. Blood samples were obtained at the time of hospital admission, before the start of intravenous therapy, and at 6 and 12 h after admission. Doppler-echocardiography was performed within 12 h after the initiation of intravenous therapy. The diagnosis of ischaemic aetiology of HF was based on a history of myocardial infarction and/or documented coronary artery disease or, when absent but an ischaemic cause suspected, on the results of a coronary angiography performed during the hospitalisation. Decisions about hospital discharge were made based on clinical evaluation, and treating physicians were blinded to cTnT values which were measured after patient's discharge by an independent laboratory.

Patient's follow-up was performed through visits at our outpatients unit or, when not possible, through telephone calls with the patient or her/his physician and/or relatives. The study was approved by our hospital's Ethics Committee. All patients signed a written informed consent form regarding their enrolment into this study.

Troponin assay

Venous blood samples were collected in tubes without anticoagulant (S-Monovette, Sarstedt), centrifuged at 3,000 rpm for 15 min and serum was immediately stored at −20°C until analysis. Cardiac troponin T was measured on an Elecsys® 2010 analyzer (Roche Diagnostics GmbH), using a third generation assay (Troponin T STAT, Roche Diagnostics). The detection limit of the assay is 0.01 ng/mL and the decision limit used for myocardial necrosis is 0.03 ng/mL. Glomerular filtration rate was calculated by the MDRD equation [22].

Patients classification

The measurement of abnormal cTnT values was entered as a categorical variable with patients classified on the basis of their cTnT levels. Each patient was classified in three different categories based on the presence of detectable or undetectable serum cTnT levels, positive or negative cTnT levels for myocardial necrosis, and, finally, on the finding of a cTnT release or not, during the hospitalisation. The first classification was performed using the limit of detection of the analytical method as cut-off: cTnT >0.01 ng/mL (detectable) versus cTnT ≤0.01 ng/mL (undetectable). The second classification was performed using cTnT levels defined as positive for myocardial necrosis: cTnT >0.03 ng/mL (positive) versus cTnT ≤0.03 ng/mL (negative). The cut-off value of 0.03 ng/mL was chosen as greater than the 10 % coefficient of variation of this measurement. Finally, cTnT release was defined by the detection of at least one positive value (>0.03 ng/mL) during hospitalisation associated with negative cTnT levels at baseline [23]. These patients were compared to those with no cTnT release, regardless of the presence of high levels at admission.

Statistical analysis

All data are shown as mean ± standard deviation unless otherwise specified. Median and interquartile range (IQR) values are shown when data did not have a normal distribution with differences between the mean and the median values. Continuous variables are compared by *T* test. Categorical variables are presented as percentages and compared by Chi-square test or Fisher exact test.

Cumulative survival estimates were calculated using the Kaplan–Meier method. Survival differences related to the main risk factors were evaluated by the long-rank method and the relative prognostic value of cTnT was calculated by the Cox univariate analysis. To assess the independent prognostic value of increased cTnT levels, this variable was entered into a multivariable model including variables traditionally related with outcomes in AHF [24–26]. A *P* value <0.05 was considered significant.

The primary endpoint of the study was all-cause death or cardiovascular (CV) hospitalisations. As in-hospital deaths could have influenced the prognostic value of variables measured during hospitalisation, namely cTnT release, we included into our study only the 198 patients who were discharged alive from hospital and excluded 5 patients who died during the hospitalisation.

The size of the study group was calculated with the primary aim of assessing the power of the measurement of serum cTnT levels to predict the incidence of major cardiovascular events (all-cause death or CV hospitalisation). Assuming an incidence of death or CV hospitalisation of 50 % we calculated that a sample size of 196 patients discharged alive from hospital would have allowed an 80 % power, with an alpha value of 0.05, to detect a hazard ratio (HR) of 0.56 with respect of the risk of events in the patients with increased serum cTnT levels versus the others.

Results

We enrolled 198 consecutive patients admitted for AHF between January 2007 and December 2008 and discharged alive from hospital. No patient was lost during follow-up. During a mean follow-up of 297 ± 233 days (median 247 days, IQR 96–480 days), 49 patients (25 %) died and 111 (56 %) died or were hospitalised for cardiovascular reasons. Four patients (2 %) underwent heart transplant.

Detectable and positive cTnT levels on admission

The demographic characteristics of the patients and their clinical and laboratory values at the time of admission according to cTnT levels are summarised in Table 1. The mean age was 68 ± 12 years, 116 patients (58 %) had an ischaemic cardiomyopathy, 68 (34 %) had no coronary artery disease (idiopathic dilated cardiomyopathy or hypertensive heart disease), and 14 patients had a primary valve disease as a cause of AHF.

Serum cTnT was detectable (>0.01 ng/mL) in 102 patients (52 %) and positive for myocardial necrosis (>0.03 ng/mL) in 78 patients (39 %). An ischaemic aetiology of HF was present in 68 patients (67 %) of those with detectable cTnT and in 56 (72 %) of those with positive cTnT levels.

Compared with the others, patients with detectable cTnT were older, had a higher prevalence of diabetes, ischaemic heart disease (67 vs. 50 %), and a higher heart rate, serum glucose, blood urea nitrogen (BUN) and creatinine levels, a lower estimated glomerular filtration rate (eGFR) and received higher doses of i.v. furosemide and were more likely to be treated with i.v. vasodilators during the hospitalisation (Table 1).

Similar to what found for patients with detectable cTnT levels, patients with cTnT positive for myocardial necrosis (cTnT >0.03 ng/mL) were older, had a higher prevalence of ischaemic heart disease (72 vs. 50 %), hypertension and diabetes, a higher heart rate, serum glucose, BUN and creatinine levels, a lower eGFR and received higher doses of i.v. furosemide and were more likely to be treated with i.v. vasodilators during the hospitalisation.

Both detectable and positive cTnT levels were associated with a higher mortality rate. Among those with

Table 1 Patients characteristics according to cTnT levels

	All patients, $n = 198$	TnT >0.01 ng/mL, $n = 102$ (52 %)	TnT ≤0.01 ng/mL, $n = 96$ (48 %)	*P* value	TnT >0.03 ng/mL, $n = 78$ (39 %)	TnT ≤0.03 ng/mL, $n = 120$ (61 %)	*P* value	TnT release $n = 36$ (18 %)	TnT no release, $n = 162$ (82 %)	*P* value
Age (years), mean ± SD	68 ± 12	70 ± 11	66 ± 13	0.004	72 (10)	66 (12)	<0.001	71 ± 9	67 ± 12	0.053
Males *n* (%)	156 (78.8 %)	79 (77 %)	77 (80 %)	0.635	60 (77 %)	96 (80 %)	0.605	25 (69 %)	131 (80 %)	0.130
Aetiology, *n* (%)										
Idiopathic	51 (26 %)	21 (20 %)	30 (31 %)	0.002	13 (16 %)	38 (32 %)	0.003	4 (11 %)	47 (29 %)	0.088
Ischaemic	116 (58 %)	68 (67 %)	48 (50 %)		56 (72 %)	60 (50 %)		26 (72 %)	90 (56 %)	
Other	31 (16 %)	13 (13 %)	18 (19 %)		10 (12 %)	22 (18 %)		6 (17 %)	25 (15 %)	
Hypertension, *n* (%)	116 (58 %)	64 (63 %)	52 (54 %)	0.221	53 (68 %)	63 (53 %)	0.031	26 (72 %)	90 (56 %)	0.129
Diabetes, *n* (%)	79 (40 %)	50 (49 %)	29 (30 %)	0.007	42 (54 %)	37 (31 %)	0.001	25 (69 %)	54 (33 %)	<0.001
NYHA class										
Before admission	3.5 ± 0.6	3.7 ± 0.5	3.3 ± 0.6	<0.0001	3.7 ± 0.5	3.4 ± 0.6	0.0002	3.4 ± 0.6	3.7 ± 0.6	0.023
At discharge	2.1 ± 0.2	2.2 ± 0.8	2.0 ± 0.7	0.206	2.2 ± 0.8	2.1 ± 0.7	0.677	2.2 ± 0.8	2.2 ± 0.8	0.628
s-Haemoglobine bs (g/dL), mean ± SD	12.7 ± 2	12.6 ± 2.0	12.6 ± 2.1	0.559	12.7 ± 2.2	12.7 ± 1.9	0.868	12.7 ± 2.3	12.7 ± 1.9	0.943
s-Creatinine bs (mg/dL), mean ± SD	1.6 ± 0.8	1.8 ± 0.8	1.5 ± 0.7	0.003	1.9 ± 0,9	1.5 ± 0.7	0.002	1.9 ± 0.9	1.6 ± 0.8	0.011
s-BUN bs (mg/dL), mean ± SD,	86 ± 51	98 ± 52	74 ± 46	<0.001	98 ± 53	78 ± 48	0.006	103 ± 45	82 ± 51	0.030
GFR bs (mL/min), mean ± SD	59.4 ± 40.5	52.7 ± 45.2	66.6 ± 33.6	0.015	52.4 ± 50.2	63.9 ± 32.1	0.049	45.8 ± 22.9	62.4 ± 54.4	0.026
s-Sodium bs (mEq/L), mean ± SD	138 ± 3.8	138 ± 4	138 ± 4	0.781	138 ± 4	138 ± 4	0.944	138 ± 4	138 ± 4	0.824
s-Potassium bs (mEq/L), mean ± SD	4.2 ± 0.6	4.3 ± 0.6	4.2 ± 0.5	0.550	4.3 ± 0.6	4.2 ± 0.5	0.284	4.3 ± 0.6	4.2 ± 0.6	0.747
s-Glucose bs (mg/dL), mean ± SD	170 ± 81,	192 ± 86	147 ± 68	<0.001	205 ± 89	148 ± 66	<0.001	222 ± 95	158 ± 72	<0.001
s-Bilirubine bs (mg/dL), mean ± SD	0.99 ± 0.61	0.92 ± 0.64	1.08 ± 0.58	0.099	0.91 ± 0.66	1.05 ± 0.57	0.137	0.96 ± 0.80	1.0 ± 0.56	0.717
EF bs (%), mean ± SD	30.7 ± 12.6	30 ± 12	31 ± 13	0.407	30 ± 13	31 ± 13	0.739	29 ± 10	31 ± 12	0.623
Mitral regurgitation bs, *n* (%)										
Absent	14 (7 %)	7 (7 %)	7 (7 %)	0.498	6 (8 %)	8 (7 %)	0.856	1 (3 %)	13 (8 %)	0.636
Mild–moderate	89 (45 %)	43 (42 %)	46 (48 %)		34 (43 %)	55 (46 %)		17 (47 %)	72 (44 %)	
Medium–severe	95 (48 %)	42 (41 %)	43 (45 %)		38 (49 %)	57 (47 %)		18 (50 %)	60 (37 %)	
ACE-inhibitors, *n* (%)	106 (54 %)	51 (50 %)	55 (57 %)	0.3039	39 (49 %)	67 (57 %)	0.4213	14 (39 %)	92 (57 %)	0.0514
Angiotensin receptor blockers, *n* (%)	31 (16 %)	13 (13 %)	18 (19 %)	0.2452	9 (12 %)	22 (18 %)	0.1986	5 (14 %)	26 (16 %)	0.7469
Beta-blockers bs, *n* (%)	129 (65 %)	60 (59 %)	69 (72 %)	0.0541	44 (56 %)	85 (71 %)	0.0374	25 (69 %)	104 (64 %)	0.5501
Antialdosterone agents bs, *n* (%)	91 (46 %)	45 (44 %)	46 (48 %)	0.5919	31 (40 %)	60 (50 %)	0.1571	19 (53 %)	72 (44 %)	0.3641
HR bs (bpm) mean ± SD	90.4 ± 23.6	95 ± 24	85 ± 22	0.003	96 ± 24	87 ± 22	0.004	99 ± 25	89 ± 23	0.019
SBP bs (mmHg) mean ± SD	129.9 ± 35.6	134 ± 42	125 ± 27	0.112	138 ± 43	125 ± 29	0.010	137 ± 38	128 ± 35	0.208
Iv furosemide (mg/24 h) mean ± SD	375 ± 331	457 ± 405	287 ± 195	<0.001	513 ± 436	285 ± 195	<0.001	513 ± 388	344 ± 311	0.005
Iv nitrate or Nitroprusside *n* (%)	96 (48.5 %)	60 (59 %)	36 (38 %)	0.003	53 (68 %)	43 (36 %)	<0.001	28 (77 %)	68 (42 %)	<0.001
Dopamine *n* (%)	66 (33 %)	39 (38 %)	27 (28 %)	0.131	32 (41 %)	34 (28 %)	0.064	15 (42 %)	51 (32 %)	0.241
Inotropic agents *n* (%)[a]	47 (23.7 %)	26 (25 %)	21 (22 %)	0.550	19 (24 %)	28 (23 %)	0.868	9 (25 %)	38 (23 %)	0.844

[a] This includes patients on dobutamine or phosphodiesterase inhibitors (enoximone) or levosimendan

detectable cTnT levels there were 32 deaths (31 %), compared to 17 deaths (18 %) in those without detectable troponin. Similarly, among those with evidence of myocardial necrosis, there were 27 deaths (35 %) compared to 22 deaths (18 %) amongst those without myocardial necrosis. Similar trends were found for the combined endpoint of all-cause death or cardiovascular hospitalisation. For detectable cTnT the combined end-point occurred in 63 patients (62 %) with detectable cTnT versus 48 patients (50 %) without detectable troponin. The combined endpoint occurred in 50 patients (64 %) with myocardial necrosis, versus 61 patients (51 %) without myocardial necrosis. Death and hospitalisation rates according to cTnT levels are outlined in Table 2. Cumulative 1-year cardiovascular hospitalisation-free survival curves are shown in Figs. 1 and 2.

Troponin release

Thirty-six (18 %) of the studied patients had a cTnT release during hospitalisation. Twenty-six of them (72 %) had concomitant coronary artery disease. When compared to the others, patients with cTnT release were older, had higher prevalence of diabetes and renal dysfunction, higher serum BUN and creatinine levels and lower GFR. They also had higher heart rate and received higher doses of i.v. furosemide and were more likely to be treated with i.v. vasodilators during the hospitalisation (Table 1).

Death for any cause occurred in 13 patients with cTnT release (36 %) compared to 36 (22 %) in those without, while the combined end-point of all-cause death or cardiovascular hospitalisation occurred in 27 (75 %) versus 84 (52 %) patients ($P = 0.011$) (Table 1). Cumulative 1-year hospitalisation-free survival rate was 10 % amongst the patients with cTnT release, versus 42 % in the others ($P < 0.001$) (Fig. 3). Among the 36 patients with cTnT release, 10 had their peak value at 6 h with a decrease at the 12-h measurement. No difference was found between this last subgroup of patients and the others with cTnT release with respect of any clinical variable and outcomes.

Multivariable analysis

Both detectable and positive cTnT levels and cTnT release were entered into a multivariable Cox regression model including all the variables significant at univariable analysis. The variables selected as predictive for all-cause death or cardiovascular hospitalisation were cTnT release, treatment with inotropic agents, and eGFR (Table 3). Kaplan–Meier survival curves for patients subdivided on the basis of cTnT release and treatment with inotropic agents are shown in Fig. 4.

Table 2 Patient outcomes according to cTnT levels

	All	TnT >0.01 ng/mL	TnT ≤0.01 ng/mL	*P* value	TnT >0.03 ng/mL	TnT ≤0.03 ng/mL	*P* value	TnT release	TnT no-release	*P* value
Death, *n* (%)	49 (25 %)	32 (31 %)	17 (18 %)	0.026	27 (35 %)	22 (18 %)	0.009	13 (36 %)	36 (22 %)	0.081
Death or CV hospitalisation, *n* (%)	111 (56 %)	63 (62 %)	48 (50 %)	0.096	50 (64 %)	61 (51 %)	0.066	27 (75 %)	84 (52 %)	0.011
1-year hospitalisation-free survival probability (%)	36 %	27 %	46 %	0.020	26 %	34 %	0.020	10 %	42 %	<0.001

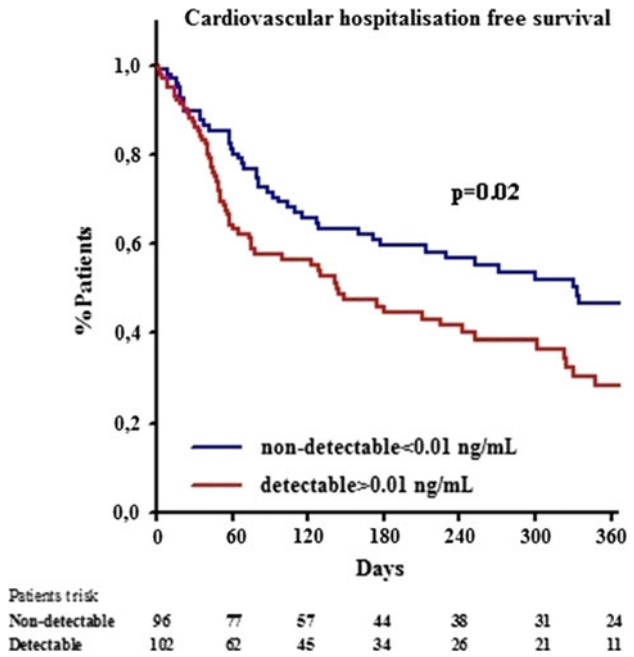

Fig. 1 Kaplan–Meier cardiovascular hospitalisation-free survival curves of the patients with detectable and undetectable cTnT levels at the time of admission to hospital

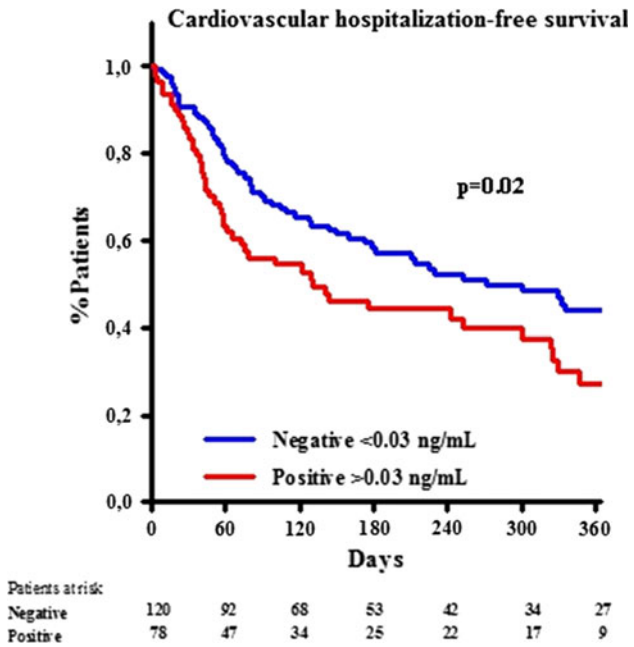

Fig. 2 Kaplan–Meier cardiovascular hospitalisation-free survival curves of the patients with cTnT levels positive or negative for myocardial necrosis at the time of admission to hospital

Discussion

Our study shows that a high proportion of patients admitted for AHF has an increase in cTnT levels with 52 % of our patients with detectable cTnT levels, 39 % of the patients

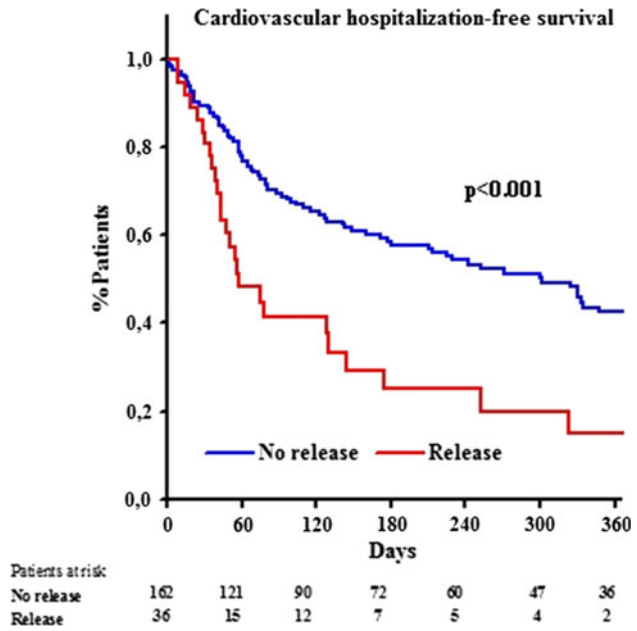

Fig. 3 Kaplan–Meier cardiovascular hospitalisation-free survival curves of the patients subdivided on the basis of cTnT release

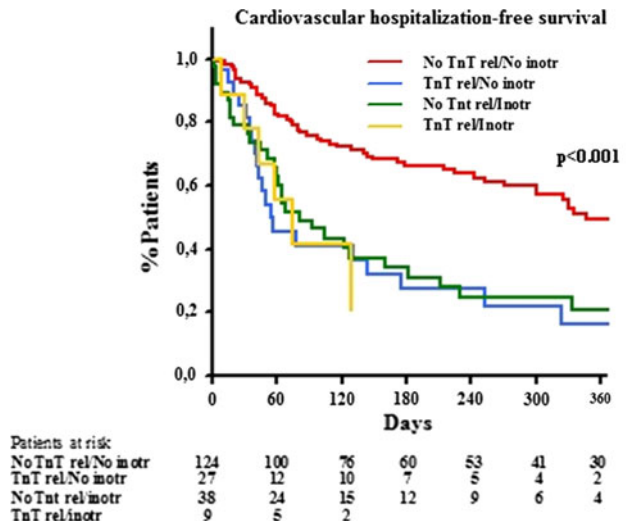

Fig. 4 Kaplan–Meier cardiovascular hospitalisation-free survival curves of the patients subdivided on the basis of cTnT release administration of i.v. inotropes during the initial hospitalisation

with levels positive for acute myocardial infarction and 18 % of the patients with levels initially negative who then become positive for myocardial necrosis during the hospitalisation (cTnT release). Patients with increased cTnT levels had a higher heart rate, were more likely to have an ischaemic aetiology of AHF, had greater comorbidities (hypertension, diabetes, and renal dysfunction), and were more likely to receive i.v. vasodilators during the hospitalisation. Patients with increased cTnT levels had higher rates of mortality and with respect to cTnT release

Table 3 Results of Cox univariable and multivariable analysis for primary endpoint all-cause death or CV hospitalisations

	Univariable analysis			Multivariable analysis[a]		
	HR	95 % CI	*P* value	HR	95 % CI	*P* value
TnT >0.01 μg/L	1.513	1.006–2.28	0.047			
TnT >0.03 μg/L	1.477	0.986–2.21	0.059			
TnT release	1.83	1.202–2.797	0.003	1.786	1.151–2.771	0.010
Diabetes	1.59	1.089–2.312	0.017			
I.v. nitrates	1.21	0.786–1.858	0.381			
I.v. inotropic agents	2.31	1.541–3.464	<0.001	2.279	1.495–3.475	<0.001
Age >70 years	1.11	0.764–1.623	0.575			
Glucose >110 mg/dL	1.38	0.866–2.187	0.164			
Bilirubin (median)	0.76	0.496–1.164	0.201			
Heart rate (median)	1.28	0.877–1.855	0.203			
eGFR bs	0.986	0.979–0.993	<0.001	0.991	0.983–0.998	0.014
Creatinine >1.3 mg/dL	2.15	1.447–3.208	<0.001			
Ischaemic aetiology	1.65	1.108–2.446	0.015			

[a] Only the variables significant at multivariable analysis are shown

remained a significant predictor for the primary endpoint also at multivariable analysis, along with a low GFR and treatment with inotropic agents.

Our results confirm and extend previous findings that a high proportion of patients with AHF have increased cTnT levels. Our finding of detectable cTnT levels in 52 % of our patients is very close to the prevalence of 49 %, described by Biolo et al. [15] in 39 patients with AHF, as well as to the prevalence of detectable TnI of 73.9 % and TnT 43.5 % shown by Gheorghiade et al. [10]. Lower percentages (6.2–49 %) were shown by studies based on only one measurement taken at the time of admission for AHF [11, 13], and in studies in patients with chronic stable HF [7, 27, 28].

Studies using high sensitivity troponin assays have found detectable levels in a higher proportion of patients with heart failure, often close to 100 % of the patients studied [16, 17, 29]. These results are consistent with those obtained in other conditions not associated with coronary artery disease, such as supraventricular tachyarrhythmias, acute pulmonary embolism, sepsis, stroke, and strenuous exercise [30–33]. The magnitude of the increase in troponin levels is generally less and persists for a shorter period of time compared with the troponin increases associated with acute myocardial infarction. In this setting, the elevation in high sensitivity troponin levels has been generally associated with poorer outcomes with a continuous relation between the magnitude of the troponin increase and the likelihood of poorer outcomes. However, despite its clinical significance, the relation between the increase in high sensitivity troponin levels and reversible or irreversible myocardial injury is still unsettled [30]. Recently, increased serum levels of cTnT have been shown in patients with diseased skeletal muscle in the absence of cardiovascular disease and their source from the diseased skeletal muscle has been shown [34, 35]. This may be a further reason for a stable increase in cTnT levels in patients with heart failure as a skeletal muscle disease may coexist in this condition [36].

Few studies have examined the prognostic significance of serial measurements of cTnT levels. These were mainly done in ambulatory patients with chronic HF and have shown that patients who develop detectable cTnT levels [37] and who have multiple elevations of cTnT [38] have a higher risk of death or transplantation. In another study, serum TnI and BNP levels were measured on admission, discharge, and up to four consecutive days during hospitalisation in 140 patients with AHF. Increased TnI and BNP were each associated with an increased risk of death or rehospitalisation. Patients with increasing TnI during hospitalisation had increased mortality compared with patients with stable or decreasing TnI [16].

In our study, we have evaluated, the clinical significance of the occurrence of increased cTnT levels during a hospitalisation for acute HF (cTnT release), compared with the detection of high serum levels at the time of admission. This finding is potentially important as the detection of increased cTnT at the time of admission may be an index of an ongoing myocardial damage, likely related to mechanisms occurring before the hospitalisation and possibly favouring the acute decompensation. In contrast, the occurrence of cTnT release during the hospitalisation should be ascribed to mechanisms related to the episode of acute decompensation, such as the hemodynamic changes and the treatment administered for acute HF [6]. A cTnT release occurred in 18 % of our patients. Similar to the patients with detectable cTnT levels at the time of admission, also these patients had an increased risk of death or re-hospitalisation. However, interestingly, only cTnT release, but not the detection of increased cTnT at baseline,

was selected as an independent variable related with outcomes by our multivariable analysis. This finding indicates the value of serial cTnT measurements during an episode of acute HF and this is consistent with recent statements [20] and recent results [23].

Our study shows that patients with increased cTnT levels have a high prevalence of coronary artery disease, diabetes, hypertension, renal dysfunction. All these comorbidities are associated with an increased likelihood of myocardial injury. Renal dysfunction may also increase the likelihood of the detection of increased cTnT levels. However, both cTnT release and low eGFR were related with outcomes at multivariable analysis, thus showing their independent role.

The higher heart rate of patients with increased cTnT levels is consistent with the role of tachycardia as a cause of myocardial ischaemia also in the setting of AHF. It is possible that concomitant beta-blocker therapy and/or the use of other bradycardic agents may reduce the incidence of myocardial ischaemia and maybe improve patients' prognosis [39].

The role of concomitant treatment is also noteworthy. Patients with increased cTnT levels received higher doses of furosemide during the first day of hospitalisation. This is consistent with the higher prevalence of renal dysfunction and the greater severity of AHF in these patients. Our patients with increased cTnT were also more likely to be treated with i.v. vasodilators, but not with i.v. inotropes. Also in this case, concomitant treatment seems more a consequence of comorbidities found in our patients, rather than a cause of cTnT release. As coronary artery disease and hypertension were more frequent in our patients with increased cTnT levels, they were also more likely to be treated with vasodilators and less likely to receive inotropes which are known to be associated with a worse prognosis in ischaemic patients [40]. However, our data do not exclude the hypothesis that the drop of blood pressure associated with excessive vasodilator therapy may have favoured myocardial ischaemia in some patients. Untoward effects of vasodilators have been shown also in previous studies [41].

The strong association of increased cTnT levels with poorer outcomes suggest that myocardial damage, as well as renal dysfunction and administration of inotropic agents, may be a mechanism which favours the progression of cardiac dysfunction and causes the poor prognosis of the patients with AHF. However, our data do not allow excluding that cTnT, as well as other variables related with prognosis, is just an epiphenomenon of more severe AHF.

One limitation of our study is the lack of measurement of natriuretic peptides (NPs) plasma levels. B-type NP and Nt-proBNP are markers of myocytes strain and increased intracardiac pressures and are well established tools for the diagnosis of heart failure and the prognostic assessment of these patients. High NPs levels at the time of hospitalisation for acute heart failure are independent predictors of in-hospital mortality, [42]; length of in-hospital stay [41]; and post-discharge mortality [43]. Serial assessment of NPs levels provides further information with respect of prognosis [44], and levels measured at the time of discharge are independent predictors of poor prognosis [45, 46]. Cardiac troponins have been investigated in combination with NPs in the setting of acute heart failure. Earlier studies with second and third generation assays for cTn showed that both biomarkers are independently related with future cardiac events [47], with an additive prognostic value [12, 48, 49]. Similar conclusions were reached also in studies evaluating NP and hsTn [16, 50, 51]. This is consistent with the fact that Tn and NPs are related to different pathophysiological mechanisms: myocardial stretch and myocardial damage, respectively. Evaluation of cTn plasma levels may therefore provide useful, supplemental information independently from NPs.

Another limitation of our study is the relatively small number of patients. However, our study group is larger than in most of the previous studies and, differently from most of the previous studies, serum cTnT levels were measured serially at baseline, 6 and 12 h after hospitalisation, rather than only at the time of admission. It is likely that the study of a larger study group may have allowed a better assessment of variables related with outcomes. Because of the relatively low number of events, we have limited our multivariable analysis to only the combined end-point of death or cardiovascular hospitalisation, without assessing mortality alone.

In conclusion, our study confirms previous findings with respect of the high prevalence of increased cTnT levels in patients admitted for AHF. In addition, it shows that a significant proportion (18 %) of patients may develop cTnT release during hospitalisation. Either detectable or positive cTnT levels or cTnT release were associated with a poor prognosis but only cTnT release remained significant after adjustment for baseline variables.

References

1. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, Strömberg A, van Veldhuisen DJ, Atar D, Hoes AW, Keren A, Mebazaa A, Nieminen M, Priori SG, Swedberg K, Vahanian A, Camm J, De Caterina R, Dean V, Dickstein K, Filippatos G, Funck-Brentano C, Hellemans I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Zamorano JL, Tendera M, Auricchio A, Bax J, Böhm M, Corrà U, della Bella P, Elliott PM, Follath F, Gheorghiade M, Hasin Y, Hernborg A, Jaarsma T, Komajda M, Kornowski R, Piepoli M, Prendergast B, Tavazzi L, Vachiery JL,

Verheugt FW, Zamorano JL, Zannad F (2008) ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur J Heart Fail 10:933–989
2. Gheorghiade M, Pang PS (2009) Acute heart failure syndromes. J Am Coll Cardiol 53:557–573
3. Metra M, Brutsaert D, Dei Cas L, Gheorghiade M (2011) Acute heart failure: epidemiology, classification and pathophysiology. In: Tubaro M, Danchin N, Filippatos G, Goldstein P, Vranckx P, Zagher D (eds) The ESC textbook of intensive and acute cardiac care. Oxford University Press, Oxford/New York, pp 479–490
4. Metra M, Felker GM, Zacà V, Bugatti S, Lombardi C, Bettari L, Voors AA, Gheorghiade M, Dei Cas L (2010) Acute heart failure: multiple clinical profiles and mechanisms require tailored therapy. Int J Cardiol 144:175–179
5. Flaherty JD, Bax JJ, De Luca L, Rossi JS, Davidson CJ, Filippatos G, Liu PP, Konstam MA, Greenberg B, Mehra MR, Breithardt G, Pang PS, Young JB, Fonarow GC, Bonow RO, Acute Heart Failure Syndromes International Working Group (2009) Acute heart failure syndromes in patients with coronary artery disease early assessment and treatment. J Am Coll Cardiol 53:254–263
6. Kociol RD, Pang PS, Gheorghiade M, Fonarow GC, O'Connor CM, Felker GM (2010) Troponin elevation in heart failure prevalence, mechanisms, and clinical implications. J Am Coll Cardiol 56:1071–1078
7. Horwich TB, Patel J, MacLellan WR, Fonarow GC (2003) Cardiac troponin I is associated with impaired hemodynamics, progressive left ventricular dysfunction, and increased mortality rates in advanced heart failure. Circulation 108:833–838
8. Del Carlo CH, Pereira-Barretto AC, Cassaro-Strunz C, Latorre Mdo R, Ramires JA (2004) Serial measure of cardiac troponin T levels for prediction of clinical events in decompensated heart failure. J Card Fail 10:43–48
9. Perna ER, Macín SM, Cimbaro Canella JP, Alvarenga PM, Ríos NG, Pantich R, Augier N, Farías EF, Jantus E, Brizuela M, Medina F (2005) Minor myocardial damage detected by troponin T is a powerful predictor of long-term prognosis in patients with acute decompensated heart failure. Int J Cardiol 99:253–261
10. Gheorghiade M, Gattis Stough W, Adams KF Jr, Jaffe AS, Hasselblad V, O'Connor CM (2005) The Pilot Randomized Study of Nesiritide Versus Dobutamine in Heart Failure (PRESERVD-HF). Am J Cardiol 96(6A):18G–25G
11. Peacock WF 4th, De Marco T, Fonarow GC, Diercks D, Wynne J, Apple FS, Wu AH, ADHERE Investigators (2008) Cardiac troponin and outcome in acute heart failure. N Engl J Med 358:2117–2126
12. Metra M, Nodari S, Parrinello G, Specchia C, Brentana L, Rocca P, Fracassi F, Bordonali T, Milani P, Danesi R, Verzura G, Chiari E, Dei Cas L (2007) The role of plasma biomarkers in acute heart failure. Serial changes and independent prognostic value of NT-proBNP and cardiac troponin-T. Eur J Heart Fail 9:776–786
13. You JJ, Austin PC, Alter DA, Ko DT, Tu JV (2007) Relation between cardiac troponin I and mortality in acute decompensated heart failure. Am Heart J 153:462–470
14. Ilva T, Lassus J, Siirilä-Waris K, Melin J, Peuhkurinen K, Pulkki K, Nieminen MS, Mustonen H, Porela P, Harjola VP (2008) Clinical significance of cardiac troponins I and T in acute heart failure. Eur J Heart Fail 10:772–779
15. Biolo A, Fisch M, Balog J, Chao T, Schulze PC, Ooi H, Siwik D, Colucci WS (2010) Episodes of acute heart failure syndrome are associated with increased levels of troponin and extracellular matrix markers. Circ Heart Fail. 3:44–50
16. Xue Y, Clopton P, Peacock WF, Maisel AS (2011) Serial changes in high-sensitive troponin I predict outcome in patients with decompensated heart failure. Eur J Heart Fail 13:37–42
17. Latini R, Masson S, Anand SI et al (2007) Prognostic value of very low plasma concentrations of troponin T in patients with stable chronic heart failure. Circulation 116:1242–1249
18. Perna E, Macin SM, Cimbaro JP et al (2004) Ongoing myocardial injury in stable severe heart failure: value of cardiac troponin T monitoring for high-risk patient identification. Circulation 110:2376–2382
19. Felker GM, Pang PS, Adams KF, Cleland JG, Cotter G, Dickstein K, Filippatos GS, Fonarow GC, Greenberg BH, Hernandez AF, Khan S, Komajda M, Konstam MA, Liu PP, Maggioni AP, Massie BM, McMurray JJ, Mehra M, Metra M, O'Connell J, O'Connor CM, Pina IL, Ponikowski P, Sabbah HN, Teerlink JR, Udelson JE, Yancy CW, Zannad F, International AHFS Working Group (2010) Clinical trials of pharmacological therapies in acute heart failure syndromes: lessons learned and directions forward. Circ Heart Fail. 3:314–325
20. Thygesen K, Mair J, Katus H, Plebani M, Venge P, Collinson P, Lindahl B, Giannitsis E, Hasin Y, Galvani M, Tubaro M, Alpert JS, Biasucci LM, Koenig W, Mueller C, Huber K, Hamm C, The Study Group on Biomarkers in Cardiology of the ESC Working Group on Acute Cardiac Care (2010) Recommendations for the use of cardiac troponin measurement in acute cardiac care. Eur Heart J 31:2197–2204
21. Thygesen K, Alpert JS (2007) Joint ESC/ACCF/AHA/WHF Task Force for the redefinition of myocardial infarction. Universal definition of myocardial infarction. Eur Heart J 28:2525–2538
22. O'Meara E, Chong KS, Gardner RS, Jardine AG, Neilly JB, McDonagh TA (2006) The modification of diet in renal disease (MDRD) equations provide valid estimations of glomerular filtration rates in patients with advanced heart failure. Eur J Heart Fail 8:63–67
23. O'Connor CM, Fiuzat M, Lombardi C, Fujita K, Jia G, Davison BA, Cleland J, Bloomfield D, Dittrich HC, Delucca P, Givertz MM, Mansoor G, Ponikowski P, Teerlink JR, Voors AA, Massie BM, Cotter G, Metra M (2011) Impact of serial troponin release on outcomes in patients with acute heart failure: analysis from the PROTECT Pilot Study. Circ Heart Fail. 4:724–732
24. Fonarow GC, Adams KF Jr (2005) Abraham WT, Yancy CW, Boscardin WJ; ADHERE Scientific Advisory Committee, Study Group, and Investigators. Risk stratification for in-hospital mortality in acutely decompensated heart failure: classification and regression tree analysis. JAMA 293:572–580
25. O'Connor CM, Abraham WT, Albert NM, Clare R, Gattis Stough W, Gheorghiade M, Greenberg BH, Yancy CW, Young JB, Fonarow GC (2008) Predictors of mortality after discharge in patients hospitalized with heart failure: an analysis from the organized program to initiate lifesaving treatment in hospitalized patients with heart failure (OPTIMIZE-HF). Am Heart J 156:662–673
26. Harjola VP, Follath F, Nieminen MS, Brutsaert D, Dickstein K, Drexler H, Hochadel M, Komajda M, Lopez-Sendon JL, Ponikowski P, Tavazzi L (2010) Characteristics, outcomes, and predictors of mortality at 3 months and 1 year in patients hospitalized for acute heart failure. Eur J Heart Fail 12:239–248
27. Missov E, Calzolari C, Pau B (1997) Circulating cardiac troponin I in severe congestive heart failure. Circulation 96:2953–2958
28. Hudson MP, O'Connor CM, Gattis WA et al (2004) Implications of elevated cardiac troponin T in ambulatory patients with heart failure: a prospective analysis. Am Heart J 147:546–552
29. Frankenstein L, Remppis A, Giannitis E, Frankenstein J, Hess G, Zdunek D, Doesch A, Zugck C, Katus HA (2011) Biological variation of high sensitive troponin T in stable heart failure patients with ischemic or dilated cardiomyopathy. Clin Res Cardiol. 100:633–640

30. Agewall S, Giannitsis E, Jernberg T, Katus H (2011) Troponin elevation in coronary vs. non-coronary disease. Eur Heart J 32:404–411
31. Werdan K, Oelke A, Hettwer S, Nuding S, Bubel S, Hoke R, Russ M, Lautenschläger C, Mueller-Werdan U, Ebelt H (2011) Septic cardiomyopathy: hemodynamic quantification, occurrence, and prognostic implications. Clin Res Cardiol. 100:661–668
32. Mingels AM, Jacobs LH, Kleijnen VW, Laufer EM, Winkens B, Hofstra L, Wodzig WK, van Dieijen-Visser MP (2010) Cardiac troponin T elevations, using highly sensitive assay, in recreational running depend on running distance. Clin Res Cardiol. 99:385–391
33. Post F, Mertens D, Sinning C, Peetz D, Münzel T (2009) Decision for aggressive therapy in acute pulmonary embolism: implication of elevated troponin T. Clin Res Cardiol. 98:401–408
34. Aggarwal R, Lebiedz-Odrobina D, Sinha A, Manadan A, Case JP (2009) Serum cardiac troponin T, but not troponin I, is elevated in idiopathic inflammatory myopathies. J Rheumatol 36:2711–2714
35. Jaffe AS, Vasile VC, Milone M, Saenger AK, Olson KN, Apple FS (2011) Diseased skeletal muscle a noncardiac source of increased circulating concentrations of cardiac troponin T. J Am Coll Cardiol 58:1819–1824
36. Middlekauff HR (2010) Making the case for skeletal myopathy as the major limitation of exercise capacity in heart failure. Circ Heart Fail. 3:537–546
37. Miller WL, Hartman KA, Burritt MF, Grill DE, Rodeheffer RJ, Burnett JC Jr, Jaffe AS (2007) Serial biomarker measurements in ambulatory patients with chronic heart failure: the importance of change over time. Circulation 116:249–257
38. Miller WL, Hartman KA, Burritt MF, Grill DE, Jaffe AS (2009) Profiles of serial changes in cardiac troponin T concentrations and outcome in ambulatory patients with chronic heart failure. J Am Coll Cardiol 54:1715–1721
39. Metra M, Torp-Pedersen C, Cleland JG, Di Lenarda A, Komajda M, Remme WJ, Cas LD, Spark P, Swedberg K, Poole-Wilson PA, COMET investigators (2007) Should beta-blocker therapy be reduced or withdrawn after an episode of decompensated heart failure? Results from COMET. Eur J Heart Fail 9:901–909
40. Teerlink JR, Metra M, Zacà V, Sabbah HN, Cotter G, Gheorghiade M, Dei Cas L (2009) Agents with inotropic properties for the management of acute heart failure syndromes. Traditional agents and beyond. Heart Fail Rev 14:243–253
41. Shah MR, Hasselblad V, Tasissa G, Christenson RH, Binanay C, O'Connor CM, Ohman EM, Stevenson LW, Califf RM (2007) Rapid assay brain natriuretic peptide and troponin I in patients hospitalized with decompensated heart failure (from the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness Trial). Am J Cardiol 100(9):1427–1433
42. Fonarow GC, Peacock WF, Phillips CO, Givertz MM, ADHERE Scientific Advisory Committee and Investigators (2007) Admission B-type natriuretic peptide levels and in-hospital mortality in acute decompensated heart failure. J Am Coll Cardiol 49(19):1943–1950 Epub 2007 Apr 30
43. Januzzi JL, van Kimmenade R, Lainchbury J, Bayes-Genis A, Ordonez-Llanos J, Santalo-Bel M, Pinto YM, Richards M (2006) NT-proBNP testing for diagnosis and short-term prognosis in acute destabilized heart failure: an international pooled analysis of 1256 patients: the International Collaborative of NT-proBNP Study. Eur Heart J 27(3):330–337 Epub 2005 Nov 17
44. Cohen-Solal A, Logeart D, Huang B, Cai D, Nieminen MS, Mebazaa A (2009) Lowered B-type natriuretic peptide in response to levosimendan or dobutamine treatment is associated with improved survival in patients with severe acutely decompensated heart failure. J Am Coll Cardiol 53(25):2343–2348
45. Kociol RD, Horton JR, Fonarow GC, Reyes EM, Shaw LK, O'Connor CM, Felker GM, Hernandez AF (2011) Admission, discharge, or change in B-type natriuretic peptide and long-term outcomes: data from organized program to initiate lifesaving treatment in hospitalized patients with heart failure (OPTIMIZE-HF) linked to medicare claims. Circ Heart Fail. 4(5):628–636 Epub 2011 Jul 8
46. Bettencourt P, Azevedo A, Pimenta J, Friões F, Ferreira S, Ferreira A (2004) N-terminal-pro-brain natriuretic peptide predicts outcome after hospital discharge in heart failure patients. Circulation 110(15):2168–74 (Epub 2004 Sep 27)
47. Ishii J, Nomura M, Nakamura Y, Naruse H, Mori Y, Ishikawa T, Ando T, Kurokawa H, Kondo T, Nagamura Y, Ezaki K, Hishida H (2002) Risk stratification using a combination of cardiac troponin T and brain natriuretic peptide in patients hospitalized for worsening chronic heart failure. Am J Cardiol 89(6):691–695
48. Fonarow GC, Peacock WF, Horwich TB, Phillips CO, Givertz MM, Lopatin M, Wynne J, ADHERE Scientific Advisory Committee and Investigators (2008) Usefulness of B-type natriuretic peptide and cardiac troponin levels to predict in-hospital mortality from ADHERE. Am J Cardiol 101(2):231–237 Epub 2007 Dec 3
49. Nishio Y, Sato Y, Taniguchi R, Shizuta S, Doi T, Morimoto T, Kimura T, Kita T (2007) Cardiac troponin T vs other biochemical markers in patients with congestive heart failure. Circ J 71(5):631–635
50. Pascual-Figal DA, Manzano-Fernández S, Boronat M, Casas T, Garrido IP, Bonaque JC, Pastor-Perez F, Valdés M, Januzzi JL (2011) Soluble ST2, high-sensitivity troponin T- and N-terminal pro-B-type natriuretic peptide: complementary role for risk stratification in acutely decompensated heart failure. Eur J Heart Fail 13(7):718–725 Epub 2011 May 6
51. Alehagen U, Dahlström U, Rehfeld JF, Goetze JP (2010) Prognostic assessment of elderly patients with symptoms of heart failure by combining high-sensitivity troponin T and N-terminal pro-B-type natriuretic peptide measurements. Clin Chem 56(11):1718–1724 Epub 2010 Sep 15